Chapter 2

Folic acid reduces the risk on neural tube defects as well as other birth defects - a registry based case-control study in the Netherlands

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Abstract

Background: Besides neural tube defects (NTDs) folic acid (FA) might also protect against heart anomalies, oral clefts, urinary tract anomalies, limb reduction defects, omphalocele and anal atresia. We investigated the association of FA exposure and the occurrence of these FA sensitive defects.

Methods: With data from the EUROCAT Northern Netherlands registry, case-control analyses were performed. Cases were all isolated FA sensitive defects (N=2057) whereas controls were defined as children and foetuses with no FA sensitive defect present (N=4621). Exposure was defined as daily use of at least 0.4 mg of FA during the FA sensitive period of the foetus and two weeks prior to this period. Since not all anomalies origin in the same weeks of foetal development, this sensitive period differed per defect.

Results: This study shows a protective effect of FA for the group of FA-sensitive anomalies as a whole, but this effect is not significant anymore after adjusting for maternal age and year of birth. Furthermore, a significant effect is found for the heart anomalies in particular. The odds ratios for NTDs, urinary tract anomalies and limb reduction defects are, although not significant, indicative for a protective effect of FA.

Discussion: Our results support the positive findings of the effect of FA in other studies. This study also stresses the importance of availability of significant numbers of affected births to perform valid studies in this field.

Background

The protective effect of folic acid (FA) on neural tube defects (NTDs) is known since the early 1990s.[1,2] More recently, many studies were published on the association between FA or multivitamin use and other defects namely heart anomalies, oral clefts, urinary tract anomalies, limb reduction defects, omphalocele, and anal atresia. Some studies report a protective effect of FA or multivitamins, while others do not, as shown in an overview of Botto *et al*.[3] Using data from EUROCAT Northern Netherlands, we have investigated the possible preventive effect of FA on all seven groups of malformation mentioned above.

Methods

Case-control analyses were performed using data of all life births, still births and abortions in the EUROCAT Northern Netherlands registry between 1981 and 2000 (N=7852). The following defects were considered FA sensitive: NTDs, heart anomalies, oral clefts, urinary tract anomalies, limb reduction defects, omphalocele and anal atresia. Within these groups, some subgroups were investigated as well: spina bifida, conotruncal heart anomalies, cleft lip with or without cleft palate and cleft palate without cleft lip. Cases were defined as having an isolated FA sensitive birth defect (N=2057) and controls as all children and foetuses with no FA sensitive anomaly present, including all chromosomal and monogenic disorders (n=4621). Births with a non-isolated FA sensitive defect were excluded from the study, unless the defect is part of a syndrome (than included as control).

It takes about two weeks to reach an optimal FA blood level. We therefore defined exposure as daily use of at least 0.4 mg of FA during the FA sensitive period of the foetus and two weeks prior to this period. Because this sensitive period differs per defect, the exposure windows also differed per birth defect as shown in table 1. Exposure of controls was defined as daily use of at least 0.4 mg FA, from two weeks before conception until eight weeks after. ‘Not exposed’ was defined as reported no use of FA during the entire preconceptional and pregnancy period. Births with other exposure windows or with unknown FA use were excluded from this study (n=1931). Logistic regression was used to determine odds ratios (OR) and 95% confidence intervals (95%CI). An adjusted OR was calculated for all FA sensitive anomalies only, because of the small numbers elsewhere.

Results and discussion

In total we included 1614 cases with an isolated FA-sensitive defect with a known FA exposure. Of these cases, 5.0% were periconceptionally exposed to FA. The proportion

Table 1: Folic acid use and outcome measures in several groups of congenital anomalies.

	Exposure window*	FA / no FA	FA (%)	OR	95% CI
Controls	-2 to 8	221 / 2,912	7.1		
All FA-sensitive anomalies	variable per defect	80 / 1,534	5.0	0.69 0.77[a]	0.53 – 0.89 0.52 – 1.14[a]
NTDs	-2 to 4	16 / 213	7.0	0.75	0.44 – 1.26
Spina bifida	-2 to 4	8 / 123	6.1	0.64	0.31 – 1.33
Heart anomalies	-2 to 8	33 / 735	4.3	0.59	0.41 – 0.86
Conotruncal anomalies[b]	-8 to 8	20 / 581	3.3	0.45	0.29 – 0.72
Clefts	variable per cleft	18 / 301	5.6	1.09	0.66 – 1.80
Cleft lip (+/- cleft palate)	-2 to 7	20 / 243	7.6	0.98	0.61 – 1.57
Cleft palate (- cleft lip)	-2 to 10	5 / 57	8.1	1.60	0.63 – 4.04
Urinary anomalies	3 to 10	7 / 183	3.7	0.59	0.27 – 1.27
Limb reduction defects	-2 to 8	2 / 67	2.9	0.39	0.10 – 1.62
Omphalocele	-2 to 10	1 / 14	6.7	1.30	0.17 – 9.95
Anal atresia	-2 to 7	3 / 21	12.5	1.70	0.50 – 5.73

* expressed in weeks in relation to calculated conception date

[a] adjusted for age mother and year of birth.

[b] conotruncal anomalies: persistent truncus arteriosus, vsd (except perimembraneous), fallot, pulmonary valve anomaly, aortic valve stenosis, hypoplastic left heart syndrome, coarctation aortae, pulmonair artery anomalies and other anomalies of aortae.

exposed varies per birth defect. Of the 3133 included controls, 7.1% were exposed to FA (see table 1).

This study shows a protective effect of FA for the FA-sensitive anomalies as a whole group, but this effect is not significant anymore after adjusting for maternal age and year of birth. Furthermore, a significant effect is found for the heart anomalies in particular and the ORs for NTDs, urinary anomalies and limb reduction defects are, although not significant, indicative for a protective effect of FA. Therefore this study partly supports the positive findings of the effect of FA in other studies. If only chromosomal and monogenic anomalies are taken as controls (N=1402) instead of all non-cases, comparable results were found (not shown in table 1).

The strongest limitation of the study is the small numbers, especially regarding the exposure rates, and therefore the low power. For example, with our 229 cases of NTDs and an exposure of 7% among controls, we can detect a OR < 0.37 (α=0.05 and power of 80%).[4] The MRC trial found a 72% protective effect of FA on the recurrence1 of NTDs and

calculating from the prevalences of Czeizel and Dudas, a reduction of 43% is found for the occurrence of NTDs.[2] Several observational studies found a risk reductions between 40% and 60%.[5-8] Thus, since we only have the power to detect a reduction of >63%, the lack of significant findings on NTDs in our study might be more the result of our small numbers than of absence of a real effect of FA itself. Interpretation of our findings is therefore difficult and should take place with caution. Another limitation of the study is the lack of healthy controls. By using malformed controls recall bias is avoided but FA might have a till so far unknown protective effect on some defects included as controls in this study. This possible non-differential misclassification might bias our findings towards unity.

Although this study finds comparable results with other studies which is indicative for validity of this database, it mainly shows the importance of availability of significant numbers of births in order to execute valid studies in this field, especially if exposure rates are low as well.

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